Feeding behavior is controlled centrally by integration of homeostatic feedback (purple pathways) with hedonic motivations (green pathways). The obesity epidemic results from failure of homeostatic suppression of appetite in an environment of high availability of palatable calorie-dense food and decreasing requirement for physical activity. Lesions implicate medial hypothalamic structures, including the arcuate (ARC), ventromedial (VMh), and dorsomedial hypothalamic (DMh) nuclei, as the homeostatic satiety center, and the lateral hypothalamic area (LHA) as the center for homeostatic feeding drive. Indeed, experimental efforts are under way that direct deep brain electrodes to these regions (see figure labels marked with an asterisk [*]).

Circulating hormones including insulin, leptin, ghrelin, peptide YY (PYY), and cholecystokinin (CCK) enter the brain via median eminence to signal energy balance and enteral feeding status to pro-opiomelanocortin (POMC) and neuropeptide Y neurons (NPY) in the ARC. NPY neurons promote hunger while POMC neurons promote satiety through actions upon LHA. POMC neurons promote metabolic rate and maintain insulin sensitivity by innervating VMH, DMH, and autonomic preganglionic neurons of the brainstem and spinal cord.

Other ascending pathways include vagal afferents (communicating gastric distension and hepatic glucose and lipid content) through brainstem relays (solitary and parabrachial nuclei) that converge upon the hypothalamus. The area postrema senses circulating intestinal glucagon-like peptide-1 (GLP-1) to mediate nausea from excessive food consumption. Furthermore, sensory information from taste afferents act via brainstem innervation of the ventral posteromedial thalamus and from the olfactory bulb via the dorsomedial nucleus of the thalamus to relay olfactory/gustatory information to the opercular cortex.

LHA integrates hypothalamic and brainstem, gustatory, mesolimbic reward, and arousal inputs. LHA produces the neuropeptides orexin and melanin concentrating hormone (MCH) that promote feeding through actions upon cognitive, limbic, motor, and autonomic systems. MCH neurons also engage the nucleus accumbens to interact with reward pathways involving dopaminergic ventral tegmental area and ventral pallidum.

Functional brain imaging of feeding-related cognitive activity and overeating reveal wide neural networks involved in hedonic motivations including hypothalamus, ventral tegmentum, dorsal and ventral striatum, opercular (primary gustatory) cortex, and orbitofrontal cortex (olfactory/gustatory cortex). Of particular interest is the subgenual anterior cingulate cortex, a region that is already a target of deep brain electrodes for relief of depression (see figure label marked with a dagger [†]).

Mechanisms of hypothalamic homeostatic dysfunctions, such as central leptin and insulin resistance, have engendered exploration of novel therapies for obesity and metabolic syndrome. Altering brain activity by targeting electrodes, gene therapy, neuropeptide microinfusions, and/or other functional neuromodulatory techniques, neurosurgeons have opportunities in the future to provide unique therapies for this significant patient population.

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FOR FURTHER INFORMATION